Ex. 2118

# ELEVATED SOLUBLE INTERLEUKIN-2 RECEPTOR LEVELS IN THE SERA AND SYNOVIAL FLUIDS OF PATIENTS WITH RHEUMATOID ARTHRITIS

E. C. KEYSTONE, K. M. SNOW, C. BOMBARDIER, CHI-HSING CHANG, D. L. NELSON, and L. A. RUBIN



In a previous study, we used an enzyme-linked immunosorbent assay to measure soluble human interleukin-2 receptors (IL-2R), and found that when activated lymphocytes produce cell-associated IL-2R, they also release a soluble form of IL-2R into culture supernatants in vitro. Soluble IL-2R have also been detected circulating in vivo at low levels in the serum of healthy individuals, and at abnormal levels in a variety of diseases, particularly those where immune dysfunction is thought to play an important role. We therefore evaluated serum IL-2R levels in 77 patients with rheumatoid arthritis (RA), and compared them with levels in 46 age-matched healthy controls. Nineteen additional RA patients with concurrently obtained sera and synovial fluid (SF) samples were compared with 14 patients with osteoarthritis of the knee or hip. The serum IL-2R levels were significantly elevated in RA patients, compared with the control groups ($P < 0.0001$). Serum IL-2R levels in the RA patients did not correlate with disease activity as determined by a variety of clinical and laboratory parameters. RA SF IL-2R levels were significantly higher than corresponding RA serum IL-2R levels ($P = 0.0001$). No such difference was noted in the osteoarthritis group, where serum and SF IL-2R levels were comparable with serum levels in healthy controls. These findings support the hypothesis that in vivo lymphocyte activation plays an important role in RA; moreover, soluble IL-2R measurement in serum and SF may be a very useful way to identify patients at risk for, or manifesting, a chronic immune-mediated inflammatory arthropathy.

Evidence has accumulated to support the concept that lymphocyte activation plays a role in the pathogenesis of rheumatoid arthritis (RA) (1). Activated lymphocytes are present in large numbers at the sites of inflammation, within both synovial fluid (SF) (2,3) and tissues (2,4,5). Supportive evidence is also provided by findings of a correlation between elevated numbers of Ia+ peripheral blood T cells and synovitis (1). In addition, a striking correlation between enhanced spontaneous peripheral blood lymphocyte proliferation and more active synovitis has been demonstrated (6,7).

Lymphocyte activation by nonspecific lectins or mitogens, or by specific antigen, has been shown to be associated with the expression of newly synthesized interleukin-2 receptors (IL-2R) on the surface of T cells (8), as well as on B cells (9). Using an enzyme-linked immunosorbent assay (ELISA) to measure soluble IL-2R, studies have also revealed that in addition to the characteristic cell surface expression of IL-2R on activated peripheral blood lymphocytes, these cells release a soluble form of the IL-2R into their culture supernatants (10). In vivo studies have demonstrated measurable amounts of circulating soluble IL-2R in the sera of normal individuals and elevated levels in the sera of patients with malignant diseases (11). Soluble IL-2R was found to be released

From the Wellesley Hospital and Sunnybrook Medical Centre, Department of Medicine, University of Toronto, Toronto, Ontario, Canada, and the Metabolism Branch, National Institutes of Health, Bethesda, Maryland.

Supported in part by a grant from the Arthritis Society of Canada.

E. C. Keystone, MD, FRCP(C): University of Toronto; K. M. Snow: University of Toronto; C. Bombardier, MD, FRCP(C): University of Toronto; Chi-Hsing Chang, PhD: University of Toronto; D. L. Nelson, MD: National Institutes of Health; L. A. Rubin, MD, FRCP(C): University of Toronto and Associate, Arthritis Society of Canada.

Address reprint requests to E. C. Keystone, MD, FRCP(C), Rheumatic Disease Unit, Wellesley Hospital, 160 Wellesley Street East, Toronto, Ontario, M4Y 1J3, Canada.

Submitted for publication October 22, 1987; accepted in revised form January 11, 1988.

in large amounts by both OKT4+ T cells and OKT4− T cells following in vitro activation by mitogenic or antigenic stimuli, and is present in lesser amounts in the supernatants of Epstein-Barr virus–transformed B lymphoblastoid cell lines (12). In contrast with the transient expression of cell-associated IL-2R after in vitro lymphocyte activation, which peaks 48–72 hours poststimulation and declines thereafter to baseline levels by day 11 (8), there is an increase in cumulative supernatant levels of soluble IL-2R (10).

The expression of IL-2R on lymphocytes early in their state of activation also contrasts with the later expression of DR antigen following activation (13). This differential expression of activation antigens might explain the paradoxical finding in the peripheral blood of RA patients of a normal proportion of IL-2R–bearing T cells (ref. 14 and unpublished observations) in the face of elevated numbers of DR-bearing T cells (3). It is conceivable, however, that an accumulation of IL-2R in the serum of RA patients may reflect lymphocyte activation, either recent or remote, and might then be detected by measuring serum levels of soluble IL-2R. The present study was therefore undertaken to quantitate the level of circulating soluble IL-2R in the sera of RA patients, and to correlate these levels with the degree of clinical disease activity in these patients.

## PATIENTS AND METHODS

**Patient selection.** Ninety-six patients with definite or classic RA (15) seen at the Rheumatic Disease Unit of the Wellesley Hospital were studied. Controls consisted of 12 age-matched healthy volunteers from the Wellesley Hospital, 34 healthy volunteers from the National Institutes of Health, and 14 patients with clinically and radiologically diagnosed osteoarthritis (OA) predominantly involving knee joints. All patients were receiving nonsteroidal antiinflammatory drugs (NSAIDs). Sixteen of the RA patients were receiving NSAIDs only. The remainder were receiving the following, in addition to NSAIDs: cytotoxic agents (6 patients), prednisone (9 patients), prednisone in combination with remittive/cytotoxic agents (6 patients), and remittive agents (59 patients). The majority of patients with OA were receiving NSAIDs only.

**Clinical evaluation.** To evaluate the relationship between the serum IL-2R level and clinical disease, a number of clinical variables were examined in each patient, including: 1) disease duration; 2) functional class, according to the criteria of the American Rheumatism Association (16); 3) duration of morning stiffness (minutes); 4) number of actively inflamed joints (defined as those with stress pain, effusion, or tenderness); 5) number of effusions; 6) grip strength (mm Hg; Lansbury index) (17); 7) number of damaged joints (defined as those with deformity, >20% loss of range of motion, or bone-on-bone crepitation); 8) damage/duration index (defined as the number of damaged joints/years of disease duration); 9) number of extraarticular features; and laboratory findings, including 10) hemoglobin level, 11) absolute lymphocyte count, 12) platelet count, 13) erythrocyte sedimentation rate (ESR; Westergren), 14) latex fixation titer (by nephelometry), and 15) medications.

To more accurately assess the relationship between clinical disease activity and serum IL-2R level, 2-indices of clinical disease activity were formulated. One index (referred to as the clinical index) included the number of tender joints, number of effused joints, duration of morning stiffness, grip strength, and ESR. The second index (referred to as the laboratory index) included the hemoglobin level, absolute number of lymphocytes, platelet count, and ESR. A negative sign was attached to the hemoglobin and lymphocyte counts, to reflect an increase in disease activity with increasing values of these variables. For each patient, the clinical and the laboratory indices were calculated as follows:

$$I_i = \frac{V_{i_1}}{{}_1SD_v} \pm \frac{V_{i_2}}{{}_2SD_v} + \ldots + \frac{V_{m_i}}{{}_mSD_v}$$

where i denotes a representative patient; $I_i$ = value of the clinical or laboratory index for patient i; m denotes the number of variables in each index; $V_{i_1}, \ldots, V_{m_i}$ represent the value for each of the variables of the index for patient i, and ${}_1SD_v, \ldots, {}_mSD_v$ are the corresponding standard deviations across all patients.

**Sample preparation.** Serum or synovial fluid was stored at −70°C from the day drawn until use.

**Monoclonal antibodies.** Anti-Tac is an Ig2a murine monoclonal antibody (18,19). It has been well characterized and has been shown to bind to a 55-kd cell surface glycoprotein that is an integral part of the human IL-2R complex. 7G7/B6 (19) is a murine IgG2a monoclonal antibody that has also been shown to bind to this same 55-kd cell surface molecule at a site distinct from that recognized by IL-2 or anti-Tac.

**ELISA for soluble IL-2R.** The ELISA for soluble IL-2 was performed as described previously (10). In brief, alternate columns of the inner 60 wells of microtiter plates were coated with 150 μl of the monoclonal anti–IL-2R antibody, anti-Tac (kindly provided by Dr. T. Waldmann) and suspended in carbonate buffer (pH 9.6) at a concentration of 1 μg/ml or in buffer alone. Following overnight incubation at 4°C, the plates were washed and 100 μl of the sample was added to the coated and control wells. After a 2-hour incubation at room temperature, the plates were washed. A 1:4,000 dilution (100 μl) of fluorescein isothiocyanate (FITC)–modified 7G7/B6 (20) in phosphate buffered saline (PBS) containing Tween 20 and 1% fetal calf serum (FCS) (PBS/Tween/FCS) was added to each well. The plates were incubated for 2 hours at room temperature, washed, and 100 μl of a 1:1,000 dilution of alkaline phosphatase–conjugated rabbit anti-FITC in PBS/Tween/FCS was added to each well. The plates were incubated further for 1 hour, washed again, and *p*-nitrophenyl phosphate (1 mg/ml; Sigma, St. Louis, MO) in diethanolamine buffer (pH 9.8) was added. The absorbance of each well was then determined spectrophotometrically at optical density 405 nm. The absorbance value of the control well was subtracted from that of the experimental wells. This value was compared with absorbances determined for a standard curve generated by the addition of varying amounts of an IL-2R standard, as previ-

ously described (10). The IL-2R standard was the cell-free supernatant of an in vitro–passaged T cell line that was arbitrarily assigned a value of 1,000 IL-2R units/ml. It has been recently shown that 3 units of soluble IL-2R is the equivalent of 1 pg of purified IL-2R protein (Nelson DL: unpublished observations).

Statistical analysis. The Wilcoxon rank sum test was used to detect differences between groups in the study comparing RA patients with normal subjects. Spearman's correlation coefficients were obtained between variables of disease activity and the IL-2R level. A 2-sample *t*-test with Bonferroni's adjustment was used to test for differences between RA and OA patients, and a paired *t*-test was used for paired serum and SF samples.

## RESULTS

Evaluation of circulating soluble IL-2R levels in the sera of 77 RA and 46 healthy controls (Figure 1) revealed a significantly elevated level in the RA group relative to the healthy controls ($P < 0.0001$). Indeed, 82% (63 of 77) of the patients tested had elevated IL-2R levels; moreover, the mean level of soluble IL-2R in 20 random SF was higher than the serum levels of both the patient and control groups ($P < 0.0001$) (Figure 1).

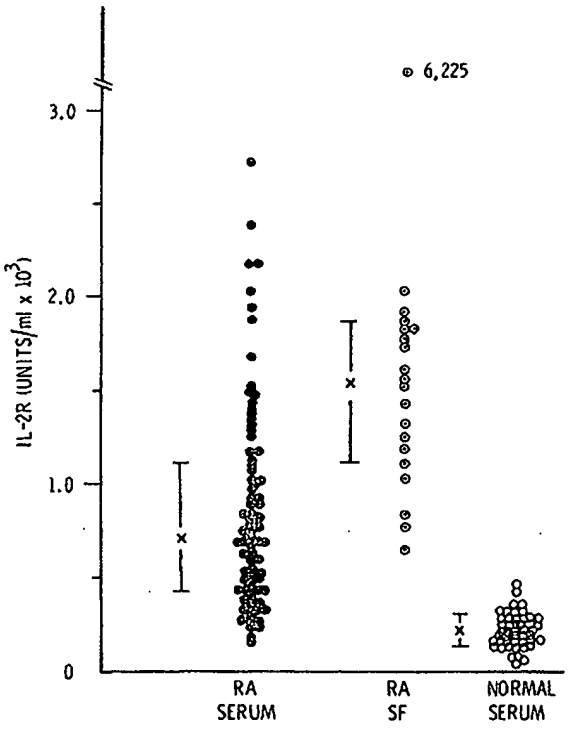


Figure 1. Levels of soluble interleukin-2 receptors (IL-2R) in sera and synovial fluids (SF) from patients with rheumatoid arthritis (RA) and in sera from healthy controls. × and bars represent the mean ± 1 SEM.

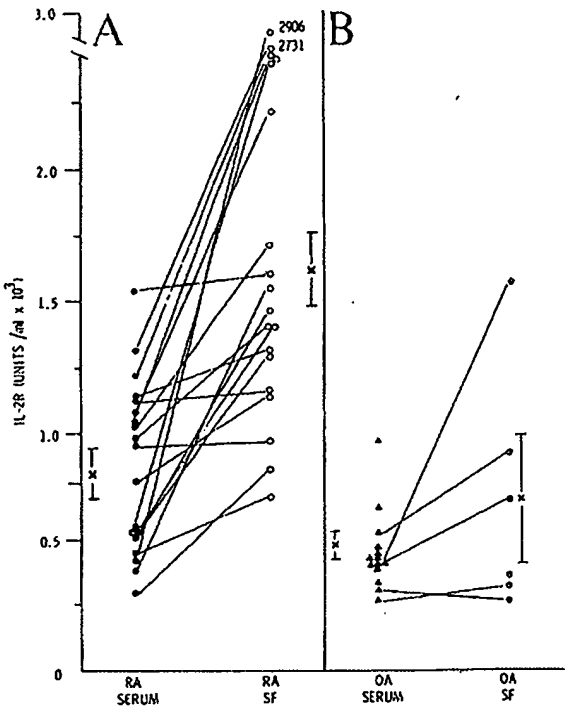


Figure 2. Levels of soluble interleukin-2 receptors (IL-2R) in A, sera and paired synovial fluids (SF) from patients with rheumatoid arthritis (RA), and B, sera and paired SF from patients with osteoarthritis (OA). × and bars represent the mean ± 1 SEM.

To compare the levels of soluble IL-2R in SF and serum, we examined sera and SF drawn simultaneously from 19 additional RA patients. We found a significantly elevated level of soluble IL-2R in SF (mean ± SEM 1,581.1 ± 151.6 units/ml) relative to sera (797.0 ± 74.2 units/ml) drawn from the same patients ($P = 0.0001$) (Figure 2A). Of note, the serum IL-2R level in this second group of RA patients was comparable with that in the first group of patients examined (mean 703.0 units/ml). Six patients had very high levels of soluble IL-2R in their SF; 5 of them had serum levels that were among the highest observed. There were no clinical features (i.e., demographic or related to disease activity) that distinguished these patients from the remainder of the study population. Data to correlate soluble IL-2R levels in fluids with the total cell count were available from 5 patients. A

strong trend was observed ($r = 0.728$), but the correlation was not significant ($P = 0.163$).

The effect of NSAIDs on the RA patients was examined by determining soluble IL-2R levels in the sera of 14 OA patients. Serum IL-2R levels were comparable with those in healthy controls (data not shown) and lower than those in the RA patient group ($P = 0.002$) (Figure 2B). In 6 OA patients, SF were obtained at the time of serum sampling. Soluble IL-2R levels in these samples were generally lower than those observed in RA SF. Thus, 4 of 6 OA fluids had IL-2R levels below the range observed in RA fluids; moreover, in contrast to the RA patients, the mean ± SEM IL-2R level in the OA SF (682.3 ± 206.3 units/ml) was comparable with that of OA serum (455.2 ± 47.3 units/ml).

To eliminate the potential cross-reactivity of circulating rheumatoid factor (RF) that may nonspecifically bind to the plate or the coating IgG monoclonal antibody (anti-Tac) in the ELISA, several serum samples with high soluble IL-2R levels, selected for the presence of high-titer RF, were repeatedly passed over a Sepharose 4B human IG affinity column (Pharmacia, Dorval, Quebec, Canada). The runoffs were collected and tested for the presence of soluble IL-2R and IgM-RF. The level of soluble IL-2R was found to be comparable with that in paired untreated samples, even when the majority of RF had been removed (data not shown).

We next examined the relationship between the soluble IL-2R levels in the serum and clinical disease activity. We evaluated this in 3 ways. We first determined whether, for each of the 15 clinical variables, there was a difference between patients with elevated IL-2R levels (>500 units/ml) and those with normal levels (<500 units/ml). We selected the level of 500 units/ml as a cutoff point because it represented a value >2 SD above the average level for the healthy control group. We also determined whether there was a correlation between the IL-2R level and the 2 indices of clinical disease activity (see Patients and Methods). The results revealed no statistically significant differences in any of the 15 clinical variables between patients with elevated IL-2R levels and those with normal levels. There was no correlation between the clinical (Figure 3) or laboratory index of disease activity and the IL-2R levels in the patient group.

Finally, we examined the serum IL-2R levels in RA patients who were in complete remission, (which was defined as lack of morning stiffness, absence of active inflammation in joints, and a normal ESR) in relation to patients with active disease. Comparing the mean ± SEM IL-2R levels in patients in remission (743.5 ± 114.9 units/ml) and in those with active disease (1,060.5 ± 129.1 units/ml), there was no significant difference ($P > 0.05$).

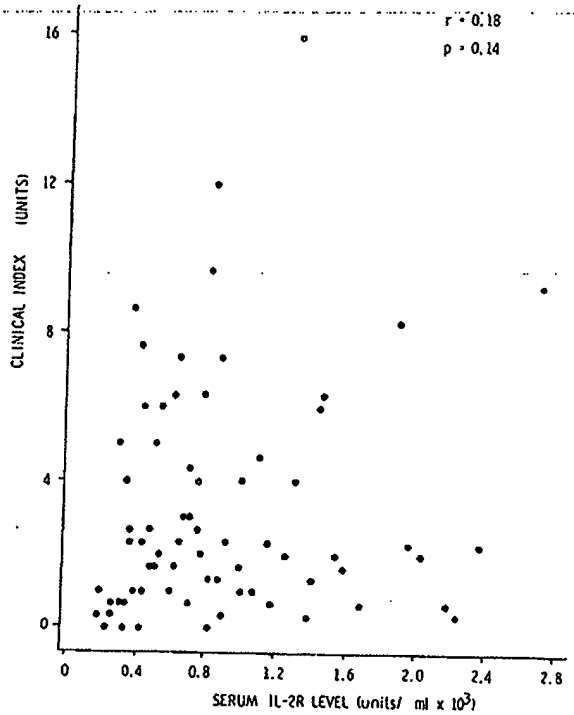


Figure 3. Correlation between the level of disease activity, as measured by the clinical index (see Patients and Methods), and the level of soluble interleukin-2 receptors (IL-2R) in the serum of patients with rheumatoid arthritis.

## DISCUSSION

This study provides additional evidence for the concept of in vivo lymphocyte activation in RA by demonstrating elevated serum levels of soluble IL-2R. The presence of this molecule in elevated levels previously has been shown to invariably accompany lymphocyte activation in vitro (10). The pathogenetic role for activated lymphocytes is further substantiated by a more marked elevation of soluble IL-2R, relative to levels in paired sera, in the synovial fluid of RA patients. Since evidence has suggested that both T cells and B cells are activated in vivo, it is likely that both lymphocyte subsets contribute to the elevated levels observed. Although optimal activation of B cells in vitro generates substantially lower levels of soluble

IL-2R relative to T cells (12), the possibility cannot be excluded that IL-2R accumulates over time in vivo as a consequence of persistent B cell activation. That T cell activation largely contributed to the elevated IL-2R levels in the synovial fluid is suggested by the predominance of DR-bearing T cells and virtual absence of B cells in RA synovial fluids (21). Moreover, the elevated soluble IL-2 levels in SF are consistent with previous reports of an increased proportion of IL-2R–bearing T cells in RA synovium (22).

These investigations of a large group of RA patients demonstrate clearly that circulating IL-2R is significantly elevated in RA patients compared with healthy controls, but that the degree of elevation does not appear to correlate with disease activity as determined by a variety of clinical and laboratory parameters. A number of explanations may be suggested for this lack of correlation, which contrasts with previous findings by others of a strong correlation between lymphocyte activation and disease activity (6,7). Serum IL-2R may accumulate over time, and thus may be less sensitive to fluctuations in clinical disease activity. Furthermore, since soluble IL-2R is a sensitive measure of lymphocyte activation, the persistent elevation may more truly reflect ongoing immune activation at cellular and humoral levels that is undetectable by present clinical and laboratory tests.

Finally, the assumption that soluble IL-2R is derived only from circulating lymphocytes may be simplistic. We have previously shown, for example, that the level of soluble IL-2R is significantly elevated in Hodgkin's disease, where lymphocytosis is not a predominant feature (11); therefore, the actual source of soluble IL-2R may be from synovial tissue cells. That this concept might pertain to rheumatoid arthritis is suggested by the marked elevation of IL-2R levels in SF and is also supported by the low levels in serum and SF in OA patients. Therefore, assaying for soluble IL-2R may be a very sensitive indicator of in situ immune activation. In turn, this may explain the lack of correlation with the classically measured disease parameters.

Despite the lack of correlation between disease activity and soluble IL-2R levels in RA sera, the levels detected in RA patients were significantly greater than those in OA patients. These results are evidence that NSAID therapy is not the cause of elevated serum IL-2R levels in RA patients, and support the concept that lymphocyte activation occurring inflammatory arthropathy contributes to the findings in RA. In particular, the significant elevation of SF IL-2R, as shown here, might be useful to identify those patients at risk for a chronic immune-mediated inflammatory arthropathy, in situations where a definitive diagnosis has otherwise not been possible.

Serial evaluations of circulating IL-2R in individual patients are currently underway, and may prove to be a more meaningful and useful application of this assay in RA. Previous studies have demonstrated the usefulness of monitoring serum IL-2R levels to assess response to therapy in a variety of malignant and infectious disorders where circulating IL-2R levels are initially elevated (23,24). Campen et al (25) have recently reported that serial measurements of serum IL-2R in a group of patients with active systemic lupus erythematosus demonstrated a decline from initial markedly elevated levels toward normal levels with clinical improvement. In addition, the level of serum IL-2R at the time of initial diagnosis has proven (e.g., in undifferentiated and lymphoblastic lymphoma) to be the most accurate predictor of disease-free survival at 5 years (26). The level in these patients was thought to be a very sensitive reflection of tumor burden, more so than currently used parameters. It is therefore possible that determining the level of serum IL-2R at the onset of rheumatoid arthritis, as well as other autoimmune disorders where immune activation is thought to play a role, might identify a subset of individuals who, by virtue of markedly elevated levels, might benefit from earlier introduction of second-line disease-remitting agents.

The physiologic significance of circulating soluble IL-2R remains unknown. It may be merely a marker of cellular immune activation, or subserve an important immunoregulatory function. Soluble IL-2R has been shown to be capable of efficiently binding IL-2 (27), with an affinity comparable with that of the low-affinity cell surface Tac or p55IL-2R molecule ($K_d = 11.1 \times 10^{-9} M$) (28). Soluble IL-2R could therefore act by binding to free IL-2, either to inhibit its interaction with cell surface receptors or, alternatively, to function as a transport protein and release IL-2 in the vicinity only of a high-affinity ($K_d = 10^{-12} M$) IL-2R complex (29). Further studies will be required to address these issues and the role of this molecule in rheumatoid arthritis.

## ACKNOWLEDGMENT

The authors acknowledge the excellent secretarial assistance of N. Jellison.

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